Pediatric lung transplantation: supply and demand

Benoit, Tobias M ; Benden, Christian

Abstract: PURPOSE OF REVIEW: Lung transplantation has become an accepted therapy in infants, children, and adolescents suffering from end-stage lung diseases, an impaired quality of life and reduced life expectancy. The aim of this review is to highlight specific aspects of pediatric lung transplantation and to give an update on recent findings. RECENT FINDINGS: Currently, over 100 lung transplant procedures are performed in children annually worldwide. Long-term success is limited by availability of donor organs and waitlist mortality pretransplant, and an increased infection risk because of immunosuppression, and most importantly late complications, such as chronic lung allograft dysfunction, medication nonadherence, and transition intricacies. SUMMARY: Specific aspects of pediatric lung transplantation will be reviewed and an update on most recent developments in the management of pediatric lung transplant recipients given.

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Tobias M. Benoit[a] *and Christian Benden*[b]

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Lung transplantation has become an accepted therapy in infants, children, and adolescents suffering from end-stage lung diseases, an impaired quality of life and reduced life expectancy. The aim of this review is to highlight specific aspects of pediatric lung transplantation and to give an update on recent findings.

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Keywords
children, chronic allograft dysfunction, extracorporeal membrane oxygenation, lung transplantation, pediatric, transition

INTRODUCTION

Lung transplantation in children has been undertaken since the 1980s, and nowadays, pediatric lung transplantation is considered as an accepted therapy option in carefully selected children with end-stage parenchymal and vascular pulmonary diseases, providing well-selected pediatric candidates a net survival benefit and improved health-related quality of life [1–4].

The 2018 International Society for Heart and Lung Transplantation (ISHLT) Thoracic Transplant Registry Report shows that currently over 100 pediatric lung transplants are performed annually worldwide, and over 2400 procedures have been carried out in children to date [5▪▪]. Nevertheless, the number of centers reporting pediatric lung transplants has remained without significant change in the last year ($n = 44$); the majority of centers have performed less than 5 transplants annually [5▪▪,6]. Traditionally, the centers performing pediatric lung transplants were mostly located in North America, Europe, and Australia, but reports of successful pediatric lung transplants in Asian and South American centers are promising [5▪▪,6–8].

Cystic fibrosis continues to be the most common primary indication for pediatric lung transplantation, but indications vary considerably by age group [5▪▪]. In infants, pulmonary hypertension and surfactant disorders are the main indications. In children between 1 and 10 years of age, cystic fibrosis and idiopathic pulmonary arterial hypertension are the most frequent underlying diseases. In adolescents (11–17 years), cystic fibrosis is still by far the most common disease leading to lung transplantation, particularly in centers outside North America [2–4,5▪▪,6,9].

Vital to comprehend that children undergoing lung transplantation present a challenge as children are not 'just small adults' [2,4]. The surgical approach is likely more challenging, and effects of immunosuppression in the developing immune system of a child, and psychosocial aspects, particularly in adolescents, have to be taken into consideration [4,10].

REFERRAL AND LISTING

In general, all children with end-stage parenchymal and vascular pulmonary disease on maximal medical therapy, a predicted life expectancy of less than

[a]Division of Internal Medicine and [b]Division of Pulmonary Medicine, University Hospital Zurich, Zurich, Switzerland

Correspondence to Christian Benden, MD FCCP, Medical Director of Lung Transplantation, Division of Pulmonary Medicine, University Hospital Zurich, CH-8091 Zurich, Switzerland. Tel: +41 44 255 41 83; e-mail: christian_benden@yahoo.de

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KEY POINTS

- Pediatric lung transplants have successfully been carried out in children of all age groups with encouraging outcomes.
- To maximize postoperative outcomes, pediatric lung transplant candidates have to be selected very carefully.
- ECMO bridging to lung transplantation is to be considered in pediatric lung transplant candidates at experienced transplant centers.
- Lung graft size reduction is considered a useful tool to overcome donor organ shortage in smaller children.
- Similar to adult lung transplantation, the development of CLAD limits the success of pediatric lung transplantation.

2 years, and a poor quality of life should be referred to a lung transplant center for transplant assessment [2,11]. Timing of referral is similar to adult practice; however, smaller children should particularly be referred as early as possible because of expected long waiting times for suitable donor organs [11].

At the assessment of every pediatric lung transplant candidate, the child and the family require to be appropriately informed and sufficiently educated. Even a child should be willing to commit to the planned transplant operation and to consent generally to the close postoperative long-term follow-up needed. Child and family support is vital and should be implemented prior to listing for transplantation if not already set up [2,4].

Overall, adherence to medical treatment needs to be evaluated prior to listing for lung transplantation. Nonadherence is a leading cause for the development of chronic allograft dysfunction (CLAD) and inferior long-term outcome posttransplant, and in particular in adolescents, it remains a well-known feature following transplantation across all solid organ types [12].

As a general rule, contraindications in pediatric lung transplantation are similar to adult practice, but relative contraindications differ between centers [2].

EXTRACORPOREAL MEMBRANE OXYGENATION AS BRIDGE TO LUNG TRANSPLANTATION

Apart from long-term invasive ventilation, extracorporeal membrane oxygenation (ECMO) has the ability to serve as a bridge to transplant in selected patients on the waiting list with rapidly advancing respiratory failure before a suitable donor organ is allocated [13,14]. In general, candidates for ECMO as bridge to transplant should be in single-organ failure with a good rehabilitation potential [11]. The consensus document by the ISHLT Council on Pulmonary Transplantation lists contraindication for ECMO as bridge to transplantation such as septic shock and multiorgan failure that are also applicable for pediatric candidates [11]. The consensus document focuses predominantly on adults but contains a section specifically addressing pediatric issues, however, in the broader term.

The use of ECMO ideally in awake pediatric candidates as bridge to transplant has recently shown to have no negative impact on the postoperative survival rates [2,6,14]. Pretransplant rehabilitation is particularly important in patients with respiratory failure requiring ECMO. Lung transplant outcomes in patients transplanted bridged on ECMO were significantly better in patients who were able to ambulate than those who were not [15,16].

Nowadays, ECMO as bridge to transplant in children is considered as a superior alternative to long-time mechanical ventilation by most transplant centers, taking potential complications of the two methods into consideration. Nevertheless, the role of ECMO in long-term bridging to transplant remains to be clearly defined [17].

DONOR ACCEPTABILITY CRITERIA IN PEDIATRIC LUNG TRANSPLANTATION

The ISHLT published donor acceptability criteria in the past, predominantly based on the adult lung transplant experience [18]. The major limit of lung transplantation is the worldwide lack of suitable donor organs. Strategies to address the shortage of donor lungs include usage of so-called marginal donor organs (or extended criteria donor organs), organ donation after circulatory death with or without ex-vivo lung perfusion as graft preparation preoperatively, and lung graft size reduction (i.e., lobar lung transplants) [19–23]. The latter is of particular interest in pediatric lung transplant candidates because of the shortage of donor organs of smaller children [21].

In the USA, donor organs are allocated through the Organ Procurement and Transplant Network (OPTN) governed by United Network for Organ Sharing (UNOS). Within its authority, children less than 12 years of age are listed according to a two-tier priority system on the basis of medical urgency, whereas patients greater than equal to 12 years are assigned a lung allocation score (LAS) similar to adult candidates [6]. The LAS, implemented in the USA in 2005, seeks to allocate organs to those

patients who will benefit most from a lung transplant and thus limit waitlist mortality [24]. Transplant candidates with higher LAS receive higher waiting list priority within geographical boundaries and matched blood type [25]. The LAS was not developed to be used in children and their data were not included in its risk-prediction models [26▪]. Therefore, the LAS models may not appropriately weigh the mortality risk of certain variables that have unique significance in pediatric patients [26▪].

Mortality rates of pediatric patients on the waiting list are higher for children aged 0–5 years of age in comparison to older children, adolescents, and adults, which raises the question if the allocation system discriminates the youngest age group, especially when listed in adult transplant centers [27]. A waitlist and transplant outcome analysis by Lancaster *et al.* [26▪] demonstrated that outcomes have significantly improved across all age groups, although the magnitude of benefit has been less for children compared with adolescents and adults.

Pediatric lung transplant candidates have historically suffered longer waiting times and higher rates of waitlist mortality than adults [6]. Over the years, lung allocation in children has undergone several modifications to improve the access of children to donor lungs. Since 2013, individual pediatric candidates are allowed to participate in the LAS under special circumstances [26▪]. Besides, OPTN has recently approved expanded sharing to direct all lungs less than 18 years old to child candidates less than 12 years old first within a certain geographic radius of 1000 mi, seeking to maximize the availability of appropriately sized pediatric donor organs to pediatric candidates [25,26▪]. Furthermore, the access of small children to donor organs was expanded by allowing ABO-incompatible lung transplants in children less than 2 years of age with low antibody titers and high wait list priority [26▪]. As with all forms of organ transplantation, donor organ availability remains the major limitation to providing lung transplants to listed pediatric candidates.

MANAGEMENT OF PEDIATRIC LUNG TRANSPLANT RECIPIENTS AND POSTTRANSPLANT OUTCOME

Immunosuppressive treatment is the foundation to prevent lung allograft rejection [28,29]. In general, the majority of children undergoing lung transplantation receive induction therapy, most commonly in the form of an interleukin-2 receptor antagonist (basiliximab) [30]. Similar to adults, children take triple maintenance immunosuppression posttransplant, typically a calcineurin inhibitor (nowadays commonly tacrolimus), a cell-cycle inhibitor (nowadays commonly mycophenolate mofetil), and corticosteroids [2,3,17]. In an effort to standardize treatment regimens, the International Pediatric Lung Transplant Collaborative has previously agreed upon unified guidelines (Goldfarb S, personal communication).

Infectious complications are common causes for morbidity and mortality in pediatric lung transplant recipients, accounting for almost 50% of deaths during the first year after transplantation [2]. Children following lung transplantation that are at high risk for infections caused by cytomegalovirus (CMV) – defined as positive recipient or donor serology – get CMV prophylaxis [31,32]. However, current practice among pediatric programs varies, even though international consensus guidelines on the management of CMV in solid organ transplant recipients were published [31]. Furthermore, pulmonary fungal infections pose a significant risk to pediatric lung transplant recipients; recently published pediatric data show a decreased 12-month posttransplant survival [33,34]. Prevention strategies are variable and center-specific, but voriconazole monotherapy was the most common regimen in pediatric cohorts [35]. The ISHLT Infectious Diseases Council has recently published guidelines for the management of fungal infections in cardiothoracic organ transplant recipients [36]. The consensus document focuses predominantly on adults but contains a section specifically addressing issues in pediatric lung transplant recipients; however, very limited data exist to respond to any of the questions related to antifungal prophylaxis and/or treatment in pediatric lung transplant recipients; thus, mostly center-specific management protocols are applied [36].

Respiratory viral infections are very common after lung transplantation, in particular, in children and associated with decreased 1-year survival [37]. Sources are often siblings or peer groups [2]. To aim to reduce the burden of vaccine preventable diseases, children should be vaccinated prior to be placed on the transplant waiting list. It is well known that vaccinations are frequently incomplete before transplantation in these severely unwell children. National vaccination guidelines should be followed; vaccination guidelines for pediatric lung transplant patients are center-specific; no consensus guidelines exist to the authors' knowledge. Vaccinations of household contacts are also highly recommended [38].

Overall, survival after pediatric lung transplantation is comparable to adults [5▪▪], although adolescent lung transplant recipients have poorer overall survival when compared with younger

children and adults, with 15–19-year-old patients experiencing the highest risk of death [39▪]. According to the most recent ISHLT Thoracic Transplant Registry Report, median survival in children after lung transplantation was 7 years for patients transplanted in the recent era (2008–2016) [5▪▪].

As in adult lung transplantation, the development of CLAD is the major hurdle to achieve better overall survival also after lung transplantation in children. Bronchiolitis obliterans syndrome (BOS), the most common form of CLAD, is the leading cause of death by 5 years following transplantation. International clinical practice guidelines for the diagnosis and management of BOS have recently been published [40]. To date, no well-proven therapy approach exists to successfully manage CLAD in lung transplant recipients, both in adult and children. Attempts include change/augmentation of immunosuppression, and use of macrolides, extracorporeal photopheresis, and total lymphoid irradiation [41,42▪▪]. Pediatric data do generally not exist. The final option for advanced lung allograft failure is lung retransplantation. Data on pediatric lung retransplantation are limited, most cases performed for CLAD-BOS and in predominantly older children [5▪▪]. Based on limited published outcome data, pediatric lung retransplants appear to be more successful if retransplantation follows a minimum of 12 months after primary transplantation in children not requiring invasive ventilator support at the time of retransplant. Children who suffer from second organ failure are regularly precluded from retransplant [43].

TRANSITION FROM PEDIATRIC TO ADULT CARE SETTING

With improving outcomes in pediatric lung transplantation, transition from pediatric to adult care is more frequent. As transition is not a single but rather a process of an adolescent lung transplant recipient being transferred to adult care providers, various aspects of other transitions of an adolescent that take place simultaneously need to be looked at (i.e., autonomy, cognition, sexuality, physical appearance, self-identity, education) [44▪]. Ideally, transition should advocate self-care and decision-making of the adolescent but also include parents/caregivers, taking into account the adolescent's chronological age, physical, and cognitive maturity. In general, transition is regarded of interest for both pediatric and adult transplant care teams [44▪]. To the authors' knowledge, no consensus on the appropriate time and execution of transition of adolescent lung transplant patients to adult transplant services exists; most commonly, the practice applied is extrapolated from transition in cystic fibrosis patients as this is to date the largest cohort of lung-transplanted adolescents.

CONCLUSION

To sum up, pediatric lung transplants have successfully been carried out in children of all age groups, including infants, with encouraging outcomes. Similar to adult lung transplantation, the development of CLAD remains the burden of lung transplantation in children and adults restricting long-term success. Potential pediatric candidates for lung transplantation should be referred early, assessed thoroughly, and selected very carefully to maximize the overall net survival benefit following pediatric lung transplantation. Specific pediatric aspects of lung transplantation are the shortage of suitable donor organs for smaller children and psychosocial aspects of adherence, in particular, in adolescents. Intricacy of transition from pediatric to adult care poses another challenge.

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Conflicts of interest

There are no conflicts of interest.

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